National Organic Standards Board
Crops Subcommittee Petitioned Material Proposal
Natamycin
June 19, 2018

Summary of Petition:

A petition was received in September 2016 to classify natamycin as an allowed nonsynthetic substance in organic crop production. The intention of the petition is to allow natamycin to be used as a post-harvest treatment on various food commodities to control fungal diseases. This product has been approved by the EPA for a wide range of uses where it prevents the germination of many types of fungal spores on mushrooms, pineapples, citrus, pome and stone fruits, cherries, avocados, kiwi, mango and pomegranate. Natamycin is described as a nonsynthetic pesticide produced by a fermentation of a naturally occurring microorganism.

Summary of Review:

The technical review (TR) requested by the Crops Subcommittee detailed the manufacturing process, the application process and use of this material in post-harvest handling. Natamycin is considered a fungistat, since it inhibits the growth of fungus, however, it can also be referred to as a fungicide, which has a broader definition which includes fungistats. Natamycin is used in nonorganic beverages, sausage, cheese and bread products to control the growth of molds and yeasts and is approved by the FDA as a direct food additive.

Natamycin is used in livestock feeds to retard the growth of the fungus that can cause mycotoxins, as well as an additive to broiler chicken water. For livestock health, it is used to suppress a variety of fungal livestock eye infections as well as ringworm, candidosis and nasal aspergillosis.

Natamycin is also used to control fungal eye, skin, mouth and vaginal conditions in humans and is therefore a useful antimicrobial for human health. There is a research study that shows concern that when natamycin is incorporated into food, such as yogurt, resistance to natamycin can occur by *Candida spp.* which have colonized the intestinal tracts of patients following natamycin treatment of fungal infections.

Natamycin is ineffective against bacteria, and regulatory definitions from FDA and USDA would classify natamycin as an antimicrobial instead of an antibiotic. The EPA, however, has a broader definition of antibiotic that would encompass natamycin (TR lines 301-332).

In 2007, natamycin was considered by the NOSB Handling Subcommittee for placement on the National List (NL) at §205.605(b) as an approved synthetic for use on baked goods to delay the growth of mold. The NOSB did not officially classify this material as a nonsynthetic or synthetic, nor did they allow this material to be used in or on organic foods.

While the petition is specifically requesting natamycin be approved for placement on the crops section of the NL for post-harvest use, if the NOSB determines natamycin to be nonsynthetic, it could then be used in a wide range of crops from mushrooms to citrus, and in organic livestock production as well. Nonsynthetic materials that are not agricultural must be listed as approved for organic processed foods on §205.605(a), so this determination as a nonsynthetic would not automatically result in its approval for use in organic handling.

During the subcommittee's review, we reached out to members of the farming, wholesale and retail produce organic community. We were not told that this product is needed from our small sample, and

we look forward to hearing more comments from the public. Some natural products retailers do not allow the use of natamycin on cheese or dairy products they sell in their stores. Natamycin would appear as a "mold inhibitor" on the retail label of the product. Since natamycin is being petitioned as a post-harvest handling material, its use would not be made known to the wholesalers, retailers or consumers of the product, since there would not be a requirement, nor a method, to label these fruits, mushrooms etc.

There was concern by the Subcommittee that this material is widely used in human health, and while cases of resistance to natamycin are not currently a human health issue, this material has only been used widely in dairy products for 10 years and less than 5 years in produce.

Specific Uses of the Substance:

The TR states the commercial applications of crop, livestock and food production can be grouped into three basic categories: 1) as an agricultural fungicide, either pre- or post-harvest, 2) as a livestock medication, and 3) as a preservative in processed foods. Natamycin is used for its antifungal properties over a wide range of pH environments and fungi. Natamycin is used most commonly to protect the surfaces of cheese and sausage against fungal development and can be incorporated into other dairy products such as yogurt, sour cream and cottage cheese. It has also been used on salad mixes to control mold. The petitioner is specifically requesting it be allowed for use as a post-harvest handling material for fruits of many types. There are no tolerances or wait periods set after use of natamycin for these fruits, with natamycin first approved for use on fruits in 2016. There are wait periods between use and sale for mushrooms and maximum levels set when incorporated into dairy products.

Approved Legal Uses of the Substance:

Canada allows biological organisms for use as crop production aids. While natamycin is not a biological organism, microbial organisms such as spinosad are permitted under this allowance and the technical review states that since natamycin is a microbial product similar to spinosad, it might be allowed under Canadian Organic Standards. Codex has a similar allowance for microbials in organic production, but only when recognized by the certification body. Natamycin is not specifically recognized as allowed under Codex. The European Union, Japan and IFOAM do not list natamycin as an approved substance on their approved materials lists. As listed above, natamycin is used in post-harvest handling for mushrooms, salad mix and a wide range of fruits as well as in and on dairy products and sausage.

Action of the Substance:

The technical review goes into detail on the action of natamycin. Natamycin interferes with the fungi's normal cell membrane function by specifically blocking ergosterol, which aids fungal cells to transfer nutrients such as glucose and amino acids through their membranes. It is most effective on fungal spores rather than mature tissue. In commercial use, it is typically added to water or wax, the type of wax was not noted in the TR.

Manufacture:

Natamycin is biosynthesized through submerged aerobic fermentation, and then extracted and purified in a post-fermentation broth through the use of solvents, pH adjustment or physical means.

There are a variety of possible other ingredients in formulations where natamycin is the active substance, to aid in its commercial use, they include:

Thickening / bulking agents: xanthan gum[iv], carrageenan[iv], methylcellulose[iv], gum Arabic[iv].
Surfactants: sodium dodecyl sulfate[iv]
Buffers: citric acid[iv], mono[iv]-, di[iv]-, tri-sodium salts of citric acid[iv], mono[iv] and disodium salts of phosphoric acid[iv]

Fillers: lactose[iv] or cellulose[iv]

Carriers: Fumed silica[iv], microcrystalline cellulose powder[iv].

pH adjustors: hydrogen chloride[iv], sulfuric acid[iv], citric acid[iv], lactic acid[iv], sodium hydroxide[iv], potassium hydroxide[iv], ammonium hydroxide[iv].

Solvents: food grade solvent such as ethanol[iv] if for agricultural or food use. Other uses include many other solvents.

Anionic surfactants: polyelectrolyte polymers (such as sodium lignosulfonate[iv]), modified styrene acrylic polymers[N], polyoxyethylene sorbitan trioleates[iv], polyoxyethylene sorbitol hexaoleates[iv], dioctyl sodium sulfosuccinate[iv], sodium salts of naphthalene sulfonates[iii].
Diluents: glycerol[iv], hexylene glycol[iii], dipropylene glycol[iii] , polyethylene glycol[iv].
Preservatives: benzoates[N] and potassium sorbate[iv].
Antifoams: silicone based antifoam agents[N], vegetable oils[N], acetylenic glycols[N], and high molecular weight adducts of propylene oxide[N].
Antifreeze: ethylene glycol[iii] , 1,2-propylene glycol[iv], 1,3-propylene glycol[N], 1,2-butanediol[N], 1,3-butanediol[iii], 1,4-butanediol[iii], 1,4-pentanediol[N], 3-methyl-1,5-pentanediol[N], 2,3-dimethyl-2,3-butanediol[N], trimethylolpropane[iii], mannitol[iii], sorbitol[iv], glycerol[iv], pentaerythritol[iii], 1,4-cyclohexanedimethanol[N], xylenol[N], bisphenol A[N].

Miscellaneous: the patent application describes applying the product with an additional coating wax.

pH adjustors: hydrogen chloride[iv], benzoic acid[iv], propionic acid[iv], sorbic acid[iv], acetic acid[iv], lactic acid[iv], or sodium hydroxide[iv].
Carriers: fumed silica[iv].
Solvents: C1-C4 alcohols[N], glacial acetic acid[iv].
Surfactants: sodium lauryl sulfate[iv], dioctyl sulfosuccinate[iv], calcium chloride[iv], non-ionic surfactants[N].

Thickening / bulking agents: hydroxypropylmethylcellulose [iv] (HPMC), carrageenan[iv], methylcellulose[iv], xanthan gum[iv], gellan gum[iv], gum Arabic[iv]

Emulsifier: lecithin[iv].

Key: * = Patent application only, not granted; iii = Present on 2004 EPA List 3; iv = Present on 2004 EPA List 4; N = Not able to confirm 2004 EPA list status.

Category 1: Classification

1. **For CROP use: Is the substance ___x__ Non-synthetic or ____ Synthetic?**
   Is the substance formulated or manufactured by a process that chemically changes a substance extracted from naturally occurring plant, animal, or mineral sources? [OFPA §6502(21)] If so, describe, using NOP 5033-1 as a guide.

   The Technical review states during the biosynthesis, extraction and purification of natamycin, the chemical makeup of the material is not changed from the original substance. The decision tree in NOP Guidance 5033-1 was used to evaluate whether or not this material is synthetic. Details are present in the TR.

2. **For CROPS: Reference to appropriate OFPA category:**
   Is the substance used in production, and does it contain an active synthetic ingredient in the following categories: [§6517(c)(1)(B)(i)]; copper and sulfur compounds; toxins derived from bacteria; pheromones, soaps, horticultural oils, fish emulsions, treated seed, vitamins and minerals; livestock parasiticides and medicines and production aids including netting, tree wraps and seals, insect traps, sticky barriers, row covers, and equipment cleansers; or (ii) is used in production and contains synthetic inert ingredients that are not classified by the Administrator of the Environmental Protection Agency as inerts of toxicological concern?

   If the NOSB determines natamycin to be nonsynthetic, there is no reason to determine a specific approved category for synthetics. Natamycin is naturally produced by bacteria, it is not listed as an inert by the EPA.

Category 2: Adverse Impacts

1. **What is the potential for the substance to have detrimental chemical interactions with other materials used in organic farming systems? [§6518(m)(1)]**
   Chemical interactions were not known beyond the issues with possible solvents used during manufacture. The TR did not state there was risk of detrimental chemical interactions with other materials used in organic farming systems.

2. **What is the toxicity and mode of action of the substance and of its breakdown products or any contaminants, and their persistence and areas of concentration in the environment? [§6518(m)(2)]**
   The TR states due to its proposed use in post-harvest handling, it is not expected there would be any significant effect on the agro-ecosystem. It would not have any direct effect on soil biological life, earthworms, mites or other macro or micro soil organisms including mycorrhizal fungi, since it is not applied to soil. The EU Food Safety Authority, had some concerns about resistance to natamycin over time, but in ten years of use, none has yet been found. However, there has been some evidence that natamycin resistance can be caused under laboratory conditions.

3. **Describe the probability of environmental contamination during manufacture, use, misuse or disposal of such substance? [§6518(m)(3)]**
   The technical review did not find any literature from the EPA, FDA, the National Institute of Environmental Health, the European Environmental Agency or other academic or independent papers addressing the issue of environmental contamination caused by the production, use, misuse or disposal of natamycin. The TR discusses possible effects that might occur through the production and use stream, through manufacture waste water or overuse, but the TR's conclusion states it is unlikely to affect the surrounding environment in a significant way. There could be negative effects on beneficial fungi if applied on non-approved agricultural crops.

4. **Discuss the effect of the substance on human health. [§6517 (c)(1)(A)(i); §6517 (c)(2)(A)(i); §6518(m)(4)].**
   At this time, the EPA determines there is a reasonable certainty that no harm will result from exposure to natamycin residues when used according to product labeling. Since bacteria is the main component of intestinal microflora in the human gut, and natamycin does not have a negative effect on bacteria, some studies have determined minimal to no negative impact when natamycin is ingested. There are other studies that show concern about the potential risk for development of fungal resistance to natamycin, or to other materials in its polyene class of

fungistats, by fungi that are problematic in human health. Natamycin is used by the medical community to treat eye, mucous membrane and skin issues by addressing fungal and yeast problems.

The use of natamycin as an antifungal agent can suppress mycotoxins that contaminate food and could be seen as beneficial to human health through this action.

The product label for natamycin to be used as an agricultural fungicide includes health warnings for the workers indicating that the product is harmful if swallowed and can cause moderate eye irritation as well as other warnings to use protective gear and activities. The TR states these warnings are probably due to the presence of other undisclosed ingredients in the formulation of the brand name products.

5. **Discuss any effects the substance may have on biological and chemical interactions in the agroecosystem, including the physiological effects of the substance on soil organisms (including the salt index and solubility of the soil), crops and livestock. [§6518(m)(5)]**
   Natamycin is being petitioned for use as a post-harvest handling material, and this use would not result in direct contact in any significant way with the agroecosystem. However, if the material is found to be nonsynthetic, it could be used in field situations in the future, if the EPA expands its biopesticide approval to this use.

6. **Are there any adverse impacts on biodiversity? (§205.200)**
   As discussed above, its limited use as a post-harvest handling material, does not result in its use in field or other situations where it may affect biodiversity in the environment. As a fungistat, it could negatively affect beneficial soil fungi if used or disposed of improperly, or if in the future it is approved as a fungicide for field applications. It is unknown if there are any negative effects on various types of wildlife or sensitive ecosystems, although it does not seem likely.

Category 3: Alternatives/Compatibility

1. **Are there alternatives to using the substance? Evaluate alternative practices as well as non-synthetic and synthetic available materials. [§6518(m)(6)]**
   The technical review describes numerous nonsynthetic and approved–for-organic-production synthetic materials, as well as hygienic activities, that can be used to control fungi in both mushroom production and post-harvest handling. Some of these are experimental, others are commonly used. It could be argued that natamycin would add another tool to the toolbox, but the case is not made that it is essential for the production of organic crops.

2. **In balancing the responses to the criteria above, is the substance compatible with a system of sustainable agriculture? [§6518(m)(7)]**
   If determined to be a nonsynthetic, natamycin could be a useful tool in controlling fungal problems in a wide variety of human and livestock foods. However, the wide use of this material to address human health issues, brings pause to the Crops Subcommittee, when considering this material for use in or on organic foods. In 2007, the NOSB did not approve this material for use on organic foods, based upon similar concerns. With other alternatives available and in use, the Subcommittee views this material as non-essential. Even if there is a just a small risk that use of this material on organic foods could result in resistant fungi or yeasts that would render natamycin no longer effective in a human or livestock medical condition, the Subcommittee sees this risk as incompatible with a system of sustainable agriculture.

Classification Motion:
Motion to classify natamycin as a nonsynthetic substance.
Motion by: Harriet Behar
Seconded by: Emily Oakley
Yes: 6 No: 0 Abstain: 1 Absent: 1 Recuse: 0

National List Motion:
Motion to add natamycin at §205.602 - nonsynthetic substances prohibited for use in organic crop production
Motion by: Harriet Behar
Seconded by: Emily Oakley
Yes: 6 No: 0 Abstain: 1 Absent: 1 Recuse: 0

Approved by Steve Ela, Crops Subcommittee Chair, to transmit to NOP August 22, 2018